

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PP20663.003	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2004/024868	International filing date (<i>day/month/year</i>) 30 July 2004 (30.07.2004)	Priority date (<i>day/month/year</i>) 31 July 2003 (31.07.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHIRON CORPORATION		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.	<p>This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 80%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/>	Box No. VI	Certain documents cited	<input checked="" type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44 <i>bis</i> .3(c) and 93 <i>bis</i> .1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44 <i>bis</i> .2).																								

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PATENT COOPERATION TREATY

REC'D 31 OCT 2005

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2004/024868

International filing date (day/month/year)
30.07.2004

Priority date (day/month/year)
31.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/09

Applicant
CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/024868

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/024868

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	18-20
	No: Claims	1-17, 21-27
Inventive step (IS)	Yes: Claims	
	No: Claims	1-27
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

1. Additional remark to item II (priority)

The priority documents pertaining to the present application were available at the time of establishing this preliminary opinion. The ISA is of the preliminary opinion that present claimed matter enjoys priority rights from the filing date of the first priority document (31.07.2003).

2. Additional remarks to item V (reasoned statement under Rule 66.2(a) (ii) with regard to novelty, inventive step or industrial applicability)

2.1 The present application is directed to immunogenic compositions comprising a combination of Group A Streptococcus pyogenes (GAS) antigens. In particular said composition comprises GAS 40 characterized by its first and/or second coiled-coil region (SEQ 12 and 13 respectively) alone or in combination with other GAS such as GAS 117, or fusion construct of said GAS antigens or antibodies specific to said GAS antigens. Said compositions are claimed for use in the treatment of S. pyogenes infection.

2.2 The present communication refers to the documents cited in the International Search Report (ISR). Said documents are numbered as in the ISR, i.e. D1 corresponds to the first document cited in the ISR. The numbering will be adhered to in the rest of the procedure.

These documents disclose, among other, the following data:

- (i) D1**, another patent from the Applicant, provides the sequences of proteins from group B and A Streptococcus, which are considered as useful antigens for vaccines, immunogenic compositions and diagnostics as well as antibodies and hybrid proteins. In particular it describes the amino sequences SEQ 9188 of 873 amino acids which comprises both present SEQ 12 (556-733) and SEQ 13 (674-704) of GAS 40, and SEQ 7465 of 113 amino acids which is 100 % identical to present sequence of GAS 117 (SEQ 34 of the new Sequence Listing, see observation under section § 4 below) (see attached sequences). It further discloses immunogenic compositions comprising the protein corresponding to each of said sequence (claim 14) as well as combination of said proteins (claim 28), use of said compositions for the treatment or prevention of infection or disease caused by S. pyogenes (claim 16), antibodies agonist said proteins (claim 4) and fusions proteins thereof (claim 18).

- (ii) **D2** describes the identification of essential genes in microorganisms. In particular the protein encoded by prokaryotic essential gene # 31978 characterized by SEQ 74375 comprises SEQ 12 and 13 of present GAS 40.

2.3 Statement with regard to novelty (Article 33 (2) PCT)

The subject-matter of **claims 1-17 and 21-27** do not meet the requirements of Article 33 (2) PCT, because it lacks novelty in view of D1 and/or D2 and/or its lack of clarity in the sense of Article 6 PCT.

- 2.31** Since D1 already discloses a protein characterized by SEQ 9188 which comprises the first and second coiled-coil regions of GAS 40 (SEQ 12 and 13 of the present application respectively), antibody against said protein as well as the use of an immunogenic composition comprising said protein for the treatment or prevention of disease caused by *S. pyogenes* (see § 2.2 i), it is novelty destroying for **claims 24-27**.

The same objection is valid in view of the protein encoded by prokaryotic essential gene # 31978 provided by D2 and characterized by SEQ 74735, because the immunogenicity of (part of) a protein is an implicit feature of a protein (PCT Guidelines, Part III, Chapter 12.04).

- 2.32** According to the definition of GAS antigen in the specification, any variant is encompassed by said term (see, f.e., p.5, I.31-40 for the definition of "a GAS 40 antigen"). Hence any of the specific antigens listed in claim 27 of D1, such as an antigen from Hepatitis A virus may be considered as a variant of GAS 117. Thus the composition of D1 comprising SEQ 9188 and said Hepatitis virus antigen falls under the scope of claims 1-14. Similarly the hybrid protein disclosed in D1 falls under the scope of claims 15-17 because its A (or B) sequence may be considered as a variant of "GAS 117". Consequently D1 is also prejudicial to novelty of **claims 1-17 and 21-23** because of the lack of clarity in the sense of Article 6 PCT of the term "GAS".

2.4 Statement with regard to inventive step (Article 33 (3) PCT)

For the sake of completeness, the attention of the Applicant is drawn to the fact that, even if some of the above novelty objections are overcome by clarifying the scope of the claims, the subject-matter of claims 1-27 does not meet the requirements of Article 33

(3) PCT, because it is not inventive over the teaching of D1 combined with the common knowledge of the person skilled in the art of immunization.

D1 is considered as the closest prior art because its aim was to solve the same problem as the present application: the provision of better immunogenic compositions for the treatment or prevention of infection by *S. pyogenes* (see § 2.2, i).

D1 differs from the present application by the solution provided to solve said problem: D1 discloses the use of immunogenic compositions comprising various characterized *S. pyogenes* antigens as well as their combinations, whereas the present application focuses on the use of composition comprising either GAS 40 alone or in combination of other GAS, or the combination of various GAS listed in claim 10 or combination of GAS antibodies.

Thus, the objective technical problem to be solved by the application may be regarded as to find alternative immunogenic compositions for the treatment or prevention of disease caused by *S. pyogenes*.

However a GAS 40 antigen comprising a first and a second coiled coil regions as well as a GAS 117 antigen (proteins characterized by SEQ 9188 and 7466 of D1 respectively), as well as combinations of GAS antigens selected among a long list of antigens are disclosed in D1. Thus the combination of specific known GAS such as GAS 40 and GAS 117 disclosed in D1 to get the same effect as disclosed in D1 (improved immunogenic response) is considered by the ISA to be an arbitrary selection, unless it presents unexpected effects or properties in relation to those described in the state of the art. The same is true for combinations of GAS antibodies because it is routine practise for a person skilled in the field of immunization to achieve passive vaccination by administering antibodies against known immunogenic antigens.

In this context, only those specific compositions embraced by the scope of present claims for which the Applicant is in a position to provide technical data showing that they induce an improved immunogenic response when compare to all the immunogenic compositions disclosed of D1, would be considered by the ISA to involve an inventive step in the sense of Article 33 (3) PCT. Since the only immunization data provided by the

specification concerned compositions comprising GAS 40 alone (example 4) (no technical data for combinations of GAS antigens and combinations of GAS antibodies), no inventive step can be acknowledged for the present claimed matter.

3. Additional remark to item VI (certain published documents, Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004078907	16.09.2004	02.03.2004	04.03.2003

This document discloses the sequence of a *S. pyogenes* hyper immune system reactive antigen Spy0269 characterized by SEQ ID N°164. Said sequence comprises SEQ 12 and 13 of GAS 40 of the present application.

4. Certain defects in the international application (item VII)

It is pointed out that the numbering of the sequence in the Sequence Listing filed on 21.04.2005 is (partially) incorrect. For example it is clear that the sequence numbered SEQ ID N°35 on page 12 of the present specification is in fact SEQ ID N°34 of the new Sequence Listing.